

REMARKS

This Amendment, filed in reply to the Office Action dated May 14, 2008, is believed to be fully responsive to each point of objection and rejection raised therein. Accordingly, favorable reconsideration on the merits is respectfully requested.

Claims 38-40, 43, 44 and 50 are rejected. Claim 38 is amended herewith to incorporate the subject matter of Claims 44-47. Claim 50 is amended solely to improve clarity. Claims 39-47 are canceled herewith without prejudice or disclaimer. No new matter is added by way of this amendment. Entry and consideration of this amendment are respectfully requested.

Claim to Priority

Applicants thank the Examiner for acknowledging Applicants' claim to foreign priority, and receipt of all the priority documents.

Withdrawn Rejections

1. Applicants thank the Examiner for withdrawal of the rejection of Claims 39, 40, 43 and 50 under 35 U.S.C. 112, second paragraph, as set forth in the Office Action mailed November 14, 2007.

2. Applicants thank the Examiner for withdrawal of the rejection of Claims 37-40, 43, 44, 48 and 50 under 35 U.S.C. 112, first paragraph, as set forth in the Office Action mailed November 14, 2007.

3. Applicants thank the Examiner for withdrawal of the rejection of Claims 37-40, 44 and 48 under 35 U.S.C. 102(b) over GenBank® GI:16565115, as set forth in the Office Action mailed November 14, 2007.

4. Applicants thank the Examiner for withdrawal of the rejection of Claims 37-40, 43, 44, 48 and 50 under 35 U.S.C. 102(b) over Random Primer 24 (New England Biolabs), as set forth in the Office Action mailed November 14, 2007.

The Rejection of Claims 38-40, 43, 44 and 50 Under 35 U.S.C. § 112 is Moot

On page 3 of the Office Action, the Examiner rejects Claims 38-40, 43, 44 and 50 under 35 U.S.C. 112, second paragraph, as being indefinite.

1. On page 3 of the Office Action, the Examiner asserts that Claim 38 is unclear in that positions 9, 81, 288 and 540, as recited in the body of the claim, are each more than 40 nucleotides away from any other of the recited positions, and accordingly, would be unable to satisfy the other requirements of the claim, namely that the primer be 40 nucleotides or less, and that the primer contain two or more of the recited positions. Claims 39, 40, 43, 44 and 50 are rejected on the same ground, as these claims ultimately depend from Claim 38.

Applicants respectfully submit that the rejection is moot in view of the amendments to Claim 38, and the cancelation of Claims 39-47.

Withdrawal of the rejection is respectfully requested.

2. On page 4 of the Office Action, the Examiner rejects Claim 50 as being indefinite for recitation of “is used,” in that this term implies a method step. The Examiner suggests that Claim 50 be amended to recite that the kit comprises the primer.

Solely to advance prosecution, and without acquiescing in the rejection, Applicants herewith amend Claim 50 to recite that “said kit comprises the primer of claim 38.” Applicants respectfully submit that the amendment overcomes the rejection.

Withdrawal of the rejection is respectfully requested.

Claims 38, 49 and 50 are Patentable Under 35 U.S.C. § 103

1. On page 5 of the Office Action, Claims 38-40 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Warner *et al.* (*Applied and Environmental Microbiology*, 65(3):1141-1144; 1999) in view of Torriani *et al.* (*Applied and Environmental Microbiology*, 67(8):3450-3454; 2001), Stine *et al.* (*Infection and Immunity*, 68(12):7180-7185; 2000) and GenBank Accession Numbers AF311535, AF311574 through AF311576, AF311578 through AF311583, AF311585 through AF311586, and AF311589 through AF311596.

In making the rejection, the Examiner alleges that Warner *et al.* disclose a method for distinguishing *Vibrio* species from one another, and for differentiating between *V. vulnificus* strains using randomly amplified polymorphic DNA analysis. The Examiner acknowledges that Warner *et al.* do not disclose primers which correspond to the claimed primers. However, in an attempt to rectify the deficiencies of Warner *et al.*, the Examiner contends that it was known in the art to design species-specific primers in order to distinguish such species, citing Torriani *et al.*

The Examiner further cites to Stine *et al.*, who allegedly disclose sequencing *recA* genes from 113 *Vibrio cholerae* strains, and closely related species, such as *Vibrio vulnificus*. The Examiner contends that one of ordinary skill in the art would possess a reasonable expectation of success in using *recA* sequence differences to discriminate *Vibrio vulnificus* from other *Vibrio* species.

Further still, the Examiner relies upon several GenBank Accession Numbers, namely AF311535, AF311574 through AF311576, AF311578 through AF311583, AF311585 through

AF311586, and AF311589 through AF311596, which allegedly represent a collection of *recA* sequences from 20 strains of *Vibrio vulnificus*. The Examiner contends that this collection of known *V. vulnificus recA* sequences would have provided the information necessary to arrive at a *V. vulnificus*-specific primer as claimed.

The Examiner contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to modify the method of Warner *et al.* according to the example of Torriani *et al.* The Examiner further contends that one of ordinary skill in the art would have been motivated to use the known *Vibrio vulnificus recA* sequences available in GenBank to design species-specific primers for the purpose of discriminating *Vibrio vulnificus* from other *Vibrio* species, since Torriani *et al.* and Stine *et al.* suggest *recA* as a marker for discrimination among species of related bacteria.

To support the rejection, the Examiner cites to the holding in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), in which the Supreme Court stated “if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person’s skill.” The Examiner contends that the same rationale applies to improving upon one prior art method based on a similar improvement to another prior art method, citing MPEP § 2143. In this regard, the Examiner contends that Torriani *et al.* recognized that species-specific differences in *recA* had allowed discrimination among other related bacteria, and so applied this knowledge to *Lactobacillus*. The Examiner further contends that the ordinary practitioner would have been motivated to apply the knowledge of Torriani *et al.* to the design of similar primers for *V. vulnificus*.

The Examiner asserts that one of ordinary skill in the art would have inevitably identified which nucleotides in *recA* were specific for *V. vulnificus*, as well as which were specific for other *Vibrio* species, and because such differences were not numerous, they would have been guided by those “specific” bases when choosing appropriate species-specific primers for *V. vulnificus*.

Applicants respectfully disagree, and traverse the rejection on the following grounds.

Initially, Applicants note that Claims 39, 40 and 44 are canceled herewith, rendering the rejection of these claims moot. Claim 38 has been amended to encompass primers containing the nucleotide sequence of any one of SEQ ID Nos: 17-20, which are exemplary primers suitable for distinguishing *Vibrio vulnificus* from other *Vibrio* species.

First, although the Examiner contends that it would have been obvious to modify the method of Warner *et al.* with that of Torriani *et al.*, citing *KSR International Co. v. Teleflex Inc.* in support of such a proposition, Applicants initially note that the present claims do not claim a generic method for distinguishing *Vibrio vulnificus* from other *Vibrio* species, but rather, are directed to *specific* primer sequences that exhibit superior specificity in such a method (and a method of using and kit thereof). The cited references do not make obvious that the claimed *primer sequences* would be of sufficient specificity to distinguish *Vibrio vulnificus* from other *Vibrio* species. To the contrary, Applicants point out that the art demonstrates the unpredictability of using species-specific primers to distinguish between closely related species. For example, Applicants note that Torriani *et al.*, as cited by the Examiner, disclose that in a previous study, although species-specific primers were designed for the purpose of distinguishing between closely related *Lactobacillus* species, *such primers lacked sufficient specificity to distinguish between closely related species*. Page 3450, paragraph 2. Thus, one of ordinary skill in the art would clearly understand from Torriani *et al.* that the identification of

oligonucleotide primers that are sufficiently specific to discriminate between closely related bacterial species is highly unpredictable, *even when the nucleotide sequences of a particular gene from closely related species are known*. Put another way, whether a given gene contains nucleotide sequences that could be used to produce oligonucleotide primers having sufficient specificity to discriminate between closely related bacterial species does not render obvious which, if any, of the species will actually work, absent experimental testing of each primer sequence, much less render obvious Applicants' claimed primer sequences. Applicants respectfully point out that, consistent with the holding in *KSR*, applying a known improvement to a known method is only obvious if the results would be predictable to one of ordinary skill in the art. Given such unpredictability, Applicants respectfully submit that the Examiner's finding of obviousness directly conflicts with the Court's holding in *KSR*. Pursuant to MPEP § 2143, to rely upon such a rationale to support a finding of obviousness, the results must be predictable to one of ordinary skill in the art. As discussed above, the art teaches the unpredictability of using species-specific primers to distinguish closely related bacterial species, and therefore, the Examiner's reliance on *KSR* is misplaced. It would be highly unpredictable, and thus non-obvious, which primer sequences would be effective in distinguishing *Vibrio vulnificus* from other *Vibrio* species. Thus, Applicants respectfully submit that the claims are not obvious for at least this reason.

Second, Applicants note that, in making the rejection, the Examiner contends that one of ordinary skill in the art would have used the cited *V. vulnificus recA* sequences from Genbank to design the claimed primers, as such sequences "would have provided the information necessary to arrive at a *V. vulnificus* primer as claimed." However, Applicants strongly disagree that one of ordinary skill in the art would have arrived at the claimed primers by relying solely on the

cited Genbank sequences. Specifically, Applicants respectfully submit that a knowledge of the nucleotide sequences of a vast array of *recA* genes not only from other *Vibrio* species, but also from *V. vulnificus* isolates, is required to arrive at a primer capable of distinguishing whether a bacterial strain is a *V. vulnificus* strain, or a closely related *Vibrio* species. Applicants point out that *V. vulnificus* is not a homogenous species, but to the contrary, represents a diverse group of heterogenous bacteria. For this reason, to design primers successful in distinguishing an array of *V. vulnificus* strains from other *Vibrio* species, a comprehensive analysis of a representative number of *V. vulnificus* and non-*V. vulnificus* *Vibrio* strains is necessary. Applicants note that the cited references do not disclose the diversity of *recA* sequences that would lead one of ordinary skill in the art to arrive at the claimed primer sequences.

Thus, Applicants respectfully submit that the claimed primers are not obvious over the cited references at least in view of the unpredictability of identifying primer sequences that are sufficiently discriminatory between closely related bacterial species, *even when the nucleotide sequences are known*, and because the cited references do not disclose sufficient diversity in *recA* gene sequences from *V. vulnificus* clinical isolates to sufficiently identify a large number of heterogenous *V. vulnificus* strains. Restated, by relying on the cited references, which only teach a narrow genus of *V. vulnificus* isolates, one of ordinary skill in the art would not arrive at primers sufficient to distinguish a large array of heterogenous *V. vulnificus* strains. The claimed primers are superior over the prior art in this regard, in that they may be used to distinguish a wide array of genetically distinct *V. vulnificus* isolates from other *Vibrio* isolates. Applicants have arrived at the claimed sequences for detecting a large array of clinically relevant heterogenous *V. vulnificus* strains by conducting a comprehensive analysis of a wide array of *V. vulnificus* and non-*V. vulnificus* *Vibrio* strains. Accordingly, Applicants' claimed primers exhibit

superior sensitivity and specificity against a large number of heterogenous *V. vulnificus* strains which is not appreciated in the prior art. The references cited by the Examiner, and the limited number of *V. vulnificus* Genbank sequences, do not disclose the diversity that exists amongst the various clinically relevant *V. vulnificus* species. For this reason, it would not have been obvious to arrive at the primer sequences as claimed merely by relying on the limited number of sequences cited in the rejection.

For the foregoing reasons, Applicants submit that the cited references do not render obvious Applicants' primer sequences as claimed.

Withdrawal of the rejection is respectfully requested.

2. On page 9 of the Office Action, the Examiner rejects Claim 43 under 35 U.S.C. 103(a) as being unpatentable over Warner *et al.* (*Applied and Environmental Microbiology*, 65(3):1141-1144; 1999) in view of Torriani *et al.* (*Applied and Environmental Microbiology*, 67(8):3450-3454; 2001), Stine *et al.* (*Infection and Immunity*, 68(12):7180-7185; 2000) and GenBank Accession Numbers AF311535, AF311574 through AF311576, AF311578 through AF311583, AF311585 through AF311586, and AF311589 through AF311596, as applied above, and further in view of Yokoyama *et al.* (US 2002/0098487).

Applicants note that Claim 43 is canceled herewith, mooted the rejection.

Withdrawal of the rejection is respectfully requested.

3. On page 10 of the Office Action, the Examiner rejects Claim 50 under 35 U.S.C. 103(a) as being unpatentable over Warner *et al.* (*Applied and Environmental Microbiology*, 65(3):1141-1144; 1999) in view of Torriani *et al.* (*Applied and Environmental Microbiology*,

67(8):3450-3454; 2001), Stine *et al.* (*Infection and Immunity*, 68(12):7180-7185; 2000) and GenBank Accession Numbers AF311535, AF311574 through AF311576, AF311578 through AF311583, AF311585 through AF311586, and AF311589 through AF311596, as applied above, and further in view of the 1988 Stratagene Catalog.

Warner *et al.*, Torriani *et al.*, Stine *et al.*, and GenBank are relied upon for the same reasons as set forth in the rejection of Claims 38-40 and 44, discussed above. However, the Examiner asserts that these references would not necessarily have directed one of ordinary skill in the art to incorporate the *Vibrio vulnificus*-specific *recA* primers suggested by the combined prior art of Warner *et al.*, Torriani *et al.*, Stine *et al.*, and GenBank into a kit.

The Examiner contends that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to incorporate the *Vibrio vulnificus*-specific *recA* primers suggested by the combined prior art of Warner *et al.*, Torriani *et al.*, Stine *et al.*, and GenBank into a kit format as discussed by Stratagene catalog.

Applicants respectively disagree, and traverse the rejection on the following grounds.

Initially, as discussed above, the cited references do not make obvious Applicants' claimed primer sequences, and the addition of the Stratagene catalog does nothing to rectify the deficiencies of the primary references. Accordingly, as the cited references do not render obvious the claimed primers, the cited references similarly cannot render obvious a kit comprising the claimed primers.

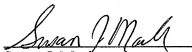
Withdrawal of the rejection is respectfully requested.

Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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CUSTOMER NUMBER

Date: August 14, 2008